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# Impact of *ERCC2* gene polymorphism on HIV-1 disease progression to AIDS among North Indian HIV patients

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**Abstract** HIV/AIDS remains to be one of the killing diseases of mankind. Host genetic response is one of the factor which determine susceptibility to HIV and disease progression to AIDS. The aim of the present study was to evaluate the impact of *ERCC2 Lyc*$^{751}$*Gln* (excision repair cross complementing rodent repair deficiency, complementation group 2) polymorphism on HIV-1 susceptibility and disease progression to AIDS, as this gene has been reported to intervene in degrading retroviral cDNA before it integrates with the host DNA. This case control study included 300 HIV seropositive cases and an equal number of HIV seronegative controls. DNA was isolated from the blood samples of study subjects and genotyping of *ERCC2* was conducted by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) method. The *Gln/Gln* genotype showed a significant variation between cases and controls ($P = 0.047$, OR 1.71, 95% CI 1.00–2.93), indicating a possible role of susceptibility in reference to controls and disease progression when compared within cases.

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**Keywords** *ERCC2* polymorphism · Disease progression · HIV 1

## Introduction

There was a total death of 2.1 million people by AIDS in the year 2007 alone. Two and a half million people were newly infected with HIV/AIDS in the same year. A total of 32.2 million people were living with HIV/AIDS worldwide in 2007. Nevertheless, it is estimated that the overall number of people living with HIV will increase in the coming years as a result of the ongoing number of new infections each year and the beneficial effects of more widely available antiretroviral therapy. In Asia, an estimated 5 million (4.1–6.2 million) people were living with HIV in 2007. The number of new infections and people who died from AIDS-related illnesses were comparatively equal in 2007 which is 380,000 (200,000–650,000) and 380,000 (270,000–490,000) respectively. National HIV infection levels are highest in South-East Asia. New HIV infections are also increasing steadily, although at a much slower pace, in populous countries such as Bangladesh and China. New more accurate estimates indicate that approximately 2.5 million (2–3.1 million) people in India were living with HIV in 2006, and that adult national HIV prevalence was 0.36%. Although the proportion of people living with HIV is lower than previously estimated, India's epidemic continues to be substantial in terms of absolute numbers [1].

The role of host genetic factor in HIV susceptibility and disease progression has been explained by a well-characterized 32-bp deletion in the host cell chemokine receptor *CCR5* [2]. When HIV binds to host cells, it uses the CD4 receptor on the surface of host immune cells together with a co receptor, mainly the CCR5 and CXCR4 chemokine

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receptors [3, 4]. Homozygous mutations for this 32-bp deletion offer almost complete protection from HIV infection through the formation of a truncated receptor preventing viral entry [5–8], and heterozygous mutations are associated with lower pre-AIDS viral loads and delayed progression to AIDS [9–16].

*ERCC2* (excision repair cross complementing rodent repair deficiency, complementation group 2), also known as Xeroderma Pigmentosum group D (*XPD*), encodes ERCC2 protein which has a helicase activity and plays a key role in nucleotide excision repair (NER) pathway [17]. Moreover, this gene appears to play a principal role in the degradation of retroviral cDNA. This XPD-dependent reduction of retroviral cDNA results in decreased successful integration events of the proviral DNA [18]. Reverse transcription of retroviral RNA genomes produce a double stranded linear cDNA molecule. A host degradation system prevents a majority of the cDNA molecules from completing the obligatory genomic integration necessary for pathogenesis. Yoder et al. [18] demonstrated that the human TFIIH complex proteins XPB (ERCC3) and XPD (ERCC2) play a principal role in the degradation of retroviral cDNA. They further explained that DNA repair-deficient *XPB* and *XPD* mutant cell lines exhibit an increase in transduction efficiency by both HIV and Moloney murine leukemia virus-based retroviral vectors. Nucleotide excision repair (NER) is a DNA damage removal pathway that is conserved from *E. coli* to humans and is triggered in response to specific types of DNA damage [19].

Till date six exonic single nucleotide polymorphisms (SNPs) have been reported in *ERCC2*, and of them, A → C polymorphism at codon 751 on exon 23 has been studied most widely and reported to modulate cancer of different types. This *ERCC2* (db SNP no. rs13181) A → C change results in amino acid substitution from lysine to glutamine. Thus, codon 751 variant leads to total rearrangement of the electronic configuration of the amino acid [20, 21]. It has been well established that the genetic disorder in the nucleotide excision repair pathway results in a number of diseases including cancer of different organs and HPV [22].

Different cohort studies of HIV-1 infected subjects have clearly indicated that the rates of progression of HIV disease may vary greatly among individuals. Although most individuals infected with HIV develop AIDS within a median period of 10 years, approximately 10% of HIV infected subjects progress to AIDS within the first 2–3 years of seroconversion (rapid progressors), and approximately 5–10% remain asymptomatic and have stable CD4/T lymphocyte counts 10 years after seroconversion (nonprogressor) [23]. A growing body of evidence suggests that host genetic factors play an important role both in susceptibility to HIV infection and progression to AIDS [24].

Among host factors that affect HIV disease progression are age, gender, route of transmission, life stress and genetic polymorphism of some genes such as *CCR5*, *CXCR4*, *HLA*, *CYP*, *SDF* do play major role in affecting disease progression from individual to individual [25–27].

The main aim of this study was to evaluate impact of *XPD* $Lyc^{751}Gln$ polymorphism on individual susceptibility to HIV-1 and its progression to AIDS in relation to other factors that affect rate of disease progression. Specifically, individual genetic differences in HIV disease progression and *ERCC2* gene were investigated in HIV seropositive cases and role of this gene in respect to susceptibility was compared with seronegative control participants.

## Materials and methods

### Study population

Written informed consent was obtained from all the cases and controls. The study was carried out after obtaining approval from the ethical committee of Postgraduate Institute of Medical Education and Research, Chandigarh, India. For this case- control study, peripheral blood samples (2–3 ml) were collected from 600 north Indian subjects during December 2007 to October 2008. These included HIV infected individuals ($n = 300$) from the immune deficient clinic of the Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh. The control blood samples ($n = 300$) were also collected from the same geographical area after they were confirmed to be seronegative for HIV by ELISA I and II tests and free from any other chronic illness. Inclusion criteria for cases were being seropositive for HIV-1 infection before starting HAART (Highly Active Anti Reteroviral therapy) and age range 18–60. Those seropositive patient who did not give written consent, age range less than 18 or greater than 60 and who did start HIV treatment were excluded from this study. Similarly the inclusion criteria for controls were age range 18–60 and being seronegative for HIV-1 test and individuals without any chronic symptom of disease. The exclusion criteria for controls was age range less than 18 or greater than 60, being seropositive for HIV-1 test, any symptom of chronic illness and failure to give written consent. All controls were healthy with no symptoms of disease. Detailed clinical data regarding age, sex, year of infection, occupation, CD4 count, stage of disease and route of transmission was obtained from the patients' record.

*ERCC2* genotyping

Genomic DNA was extracted from peripheral blood by proteinase K digestion and phenol–chloroform extraction. Genomic DNA was used to genotype *XPD* $Lys^{751}Gln$ by means of polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analysis. PCR was performed in 25 µl reaction mixture, containing 50 ng of genomic DNA 2 mM $MgCl_2$, 0.04 mM deoxynucleotide triphosphates, 1.0 U of Taq polymerase, and the Manufacturer's buffer [20 mM Tris–HCl (pH 8.4) and 50 mM KCl]. PCR condition was accomplished by initial denaturation at 94°C for 4 min was followed by 30 cycles of 30 s at 94°C, 30 s at 60°C and 1 min at 72°C, and then a final extension step of 7 min at 72°C. The 734 bp *XPD* PCR products were amplified with the primers 5′-CCTCTC CCTTTCCTCTGTTC-3′ (forward) and 5′-GGTGAGGGG GACATCT-3′ (reverse). Twenty microliter of PCR product (734 bp) (Fig. 1) was digested with 10 U of Pst I restriction enzyme and 1× buffer supplied with the enzyme (New England Bio labs, USA) at 37°C overnight. The variant allele revealed 646 bp fragment following digestion and 3% agarose gel electrophoresis, while the wild allele was not able to be digested by Pst I [28] (Fig. 2).

Statistical analysis

Chi-square analysis was utilized to test the frequencies of the genotype and alleles. Age, sex, occupation, transmission route, CD4 count, disease stage and opportunistic disease infection were tabulated for cases. The association between polymorphism of *XPD* gene with the risk of HIV was estimated by computing odds ratio (OR) and 95% confidence intervals (95% CI), using a multivariate logistic regression analysis that included several variables such as age, opportunistic infection, stage of HIV, route of transmission and CD4 count. The statistical analysis was performed using Epi-Info software (Epi-Info, version 3.5.1. Center for Disease Control and Prevention, Atlanta, GA, USA) and software SPSS version 11.5 (SPSS, Chicago, IL). Significance was set at $P < 0.05$.

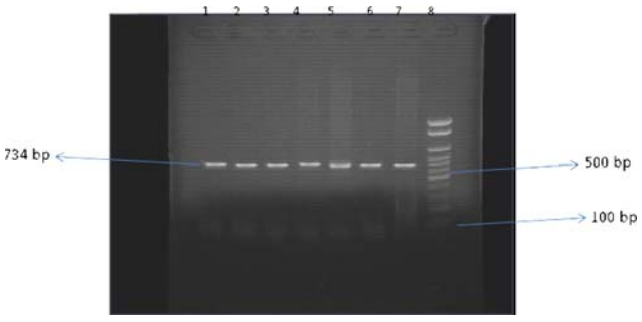


**Fig. 1** PCR amplified product of *XPD* gene of HIV seropositive subjects. *Lane 8* 100 bp DNA marker, *lane 1–7* 734 bp *XPD* PCR product

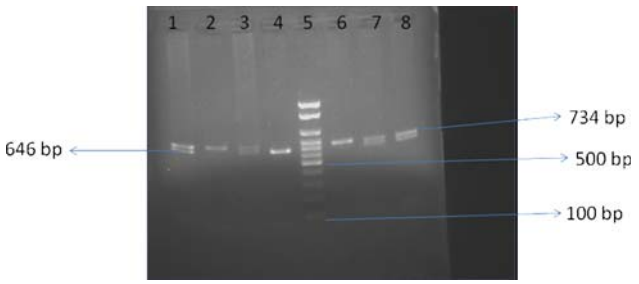


**Fig. 2** PCR-RFLP representative agarose gel of *XPD* (Pst I) digest genotype analysis of HIV seropositive subjects. *Lane 5* 100 bp DNA marker, *lane 1, 3, 7, 8 Lyc/Gln* 646 and 734 bp, *lane 2 and 6 Lyc/Lyc* 734 bp, *lane 4 Gln/Gln* 646 bp

## Results

This study analyzed the role of *XPD* $Lyc^{751}Gln$ polymorphism in risk of HIV-1 susceptibility and progression to AIDS in north Indian Population. The study included 300 cases and an equal number of controls. Although effort was made to frequency-match cases and controls by age, cases were younger in average than controls. However, there was no significant difference in the mean age between cases (mean ± SD, 35 ± 8) and controls (36 ± 10) ($P > 0.05$). There were more males in the study. Among cases, the number of men was 193 (64.3%), and that of women it was 107 (35.7%). Similarly the number of men in controls was 195 (65%) and that of women it was 105 (35%).

Of the 300 HIV patients, 9% were at stage I of HIV, 18% were at stage II, and the remaining 24.3 and 48.7% were at stages III and IV respectively. Percentage of disease stage on basis of sex is given in Table 1.

Among all the study subjects (cases), truck drivers accounted for about 21.7% followed by farmers 18.3%, labourers 8.7% and others working in different private and public sectors accounted 21.7%. Almost all women were house wives and they accounted for 29.6% of the

**Table 1** Study subjects (cases) and the stages of HIV AIDS

| Stage | Male | | Female | | Total | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| I | 18 | 9.3 | 9 | 8.4 | 27 | 9 |
| II | 32 | 16.6 | 22 | 20.6 | 54 | 18 |
| III | 48 | 24.9 | 25 | 23.3 | 73 | 24.3 |
| IV | 95 | 49.2 | 51 | 47.7 | 146 | 48.7 |
| Total | 193 | 100 | 107 | 100 | 300 | 100 |

occupation share. Of all the women cases, only eight belonged to the fourth category. Table 2 shows the category of cases on the basis of occupation.

The transmission route of HIV among cases was mostly of heterosexuality that accounted for 92.3% of the transmission, which was followed by unknown and blood transfusion accounting for 4.4 and 1.7% respectively. Acquiring HIV during sharing of contaminated needle and men who had sex with men (MSM) accounted for 1.3 and 0.3% respectively. Cases that belonged to the unknown category were those involved in more than one possible routes of transmission and did not exactly know the source of their infection.

The percentage of the *ERCC2* *Lyc*$^{751}$*Gln* genotype distribution for both cases and controls is given in Table 3. Chi-square ($\chi^2$) analysis was utilized to test the Hardy Weinberg's equilibrium, the study subjects were in accordance with this equilibrium $P > 0.05$. The percentage of the *Lyc/Lyc* genotype in controls was greater (38.7%) as compared to cases (29.7%). The *Lyc/Gln* genotype percentage was more in cases (53.6%) than in controls (48.7%). The percentage of the *Gln/Gln* genotype was 16.7% in cases as compared to 12.7% in controls. A significant variation existed among cases and controls with respect to the variant *Gln/Gln* genotype ($P = 0.047$, OR 1.71, 95% CI 1.00–2.93). The combined *Lyc/Gln* + *Gln/Gln* genotypes too showed a significant variation in cases ($P = 0.025$, OR 1.49, 95% CI 1.05–2.13). The stage of HIV and frequency of genotype at each stage is given in Table 4. The staging was done by physicians as per the WHO clinical staging of HIV disease in adults and adolescents (Version 2006). Among the total 300 study subjects, 219 were found to be at stages III and IV. The mean CD 4 count was found to be 498, 384, 259 and 116 for stages I, II, III and IV respectively. Statistically significant association was observed between the heterozygous *Lyc/Gln* and variant homozygous *Gln/Gln* genotypes and stage IV of HIV (OR 1.72, 95% CI 1.06–2.81, $P = 0.028$ and OR 2.71, 95% CI 1.43–5.18, $P = 0.0016$) respectively indicating a probable risk of accelerated disease progression. The frequencies of the three genotype of *ERCC2* were correlated with time of disease progression. Table 5 shows the distribution of the three genotypes in respect to time of disease progression for each stage. 4.48 folds of increased risk towards accelerated disease progression was observed between *Gln/Gln* genotype in 3–5 years of seroconvertors at stage IV of HIV (OR 4.48, 95% CI 1.99–10.18, $P = 0.0000979$).

**Table 2** Study subjects (cases) and their occupation

| Occupation | Male | | Female | | Total | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| Labourer | 20 | 10.4 | 6 | 5.6 | 26 | 8.7 |
| Farmer | 51 | 26.4 | 4 | 3.7 | 55 | 18.3 |
| Truck driver | 65 | 33.7 | – | – | 65 | 21.7 |
| House wife | – | – | 89 | 83.2 | 89 | 29.6 |
| Others | 57 | 29.5 | 8 | 7.5 | 65 | 21.7 |
| Total | 193 | 100 | 107 | 100 | 300 | 100 |

**Table 3** Genotype and allele frequency of *ERCC2* among study subjects

| Genotype | Cases | | Controls | | *P* value | OR (95% CI) |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | | |
| *Lyc/Lyc* | 89 | 29.7 | 116 | 38.7 | | 1 (Ref.) |
| *Lyc/Gln* | 161 | 53.6 | 146 | 48.7 | 0.055 | 1.44 (0.99–2.08) |
| *Gln/Gln* | 50 | 16.7 | 38 | 12.7 | 0.047[a] | 1.71 (1.00–2.93) |
| *Lyc/Gln* + *Gln/Gln* | 211 | 70.3 | 184 | 61.4 | 0.025[b] | 1.49 (1.05–2.13) |
| Allele = *Lyc* | 339 | 56.5 | 378 | 63 | | |
| *Gln* | 261 | 43.5 | 222 | 37 | 0.025[c] | 1.31 (1.03–1.66) |

OR was calculated by EPI-Info. version 3.5.1. (Center for Disease Control and Prevention)

*CI* confident interval, *OR* odds ratio, *Ref* reference

[a, b, c] $P < 0.05$

**Table 4** Distribution of $ERCC_2$ genotype in respect to each stage of HIV

| Stages of HIV | Genotypes of *XPD* | n/c | OR (95% CI) | *P* |
|---|---|---|---|---|
| I | *Lyc/Lyc* | 9/116 | 1.0 Ref. | 1.0 Ref. |
| | *Lyc/Gln* | 12/146 | 1.06 (0.40–2.84) | 0.91 |
| | *Gln/Gln* | 6/38 | 1.89 (0.71–5.02) | 0.22 |
| II | *Lyc/Lyc* | 22/116 | 1.0 Ref. | 1.0 |
| | *Lcy/Gln* | 29/146 | 1.05 (0.55–2.0) | 0.45 |
| | *Gln/Gln* | 3/38 | 0.46 (0.41–1.46) | 0.25 |
| III | *Lyc/Lyc* | 22/116 | 1.0 Ref. | 1.0 |
| | *Lcy/Gln* | 42/146 | 1.52 (0.83–2.79) | 0.19 |
| | *Gln/Gln* | 9/38 | 1.25 (0.48–3.16) | 0.77 |
| IV | *Lyc/Lyc* | 36/116 | 1.0 Ref. | 1.0 |
| | *Lcy/Gln* | 78/146 | 1.72 (1.06–2.81) | 0.028[a] |
| | *Gln/Gln* | 32/38 | 2.71 (1.43–5.18) | 0.0016[b] |

OR was calculated by EPI-Info version 3.5.1. (Center for Disease Control and Prevention)

*n/c* genotype at particular stage to number of control for the same genotype, *OR* odds ratio, *95% CI* confidence interval

*P* value < 0.05 significant

[a, b] $P < 0.05$

**Table 5** Genotype distribution and time of disease progression among seropositive subjects

| Year of seroconversion | Genotype | S I n/c | OR (95% CI) | S II n/c | OR (95% CI) | S III n/c | OR (95% CI) | S IV n/c | OR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| 1–2 years | *Lyc/Lyc* | 2/116 | 1.0 Ref. | 4/116 | 1.0 Ref. | 11/116 | 1.0 Ref. | 12/116 | 1.0 Ref. |
| | *Lyc/Gln* | 4/146 | 1.57 (0.29–8.44) | 13/146 | 2.45 (0.82–7.33) | 19/146 | 1.37 (0.59–3.22) | 33/146 | 2.18 (1.03–4.70) |
| | *Gln/Gln* | 1/38 | 1.51 (0.14–16.23) | 1/38 | 0.77 (0.09–6.68) | 3/38 | 0.84 (0.25–2.88) | 7/38 | 1.78 (0.58–5.33) |
| 3–5 years | *Lyc/Lyc* | 6/116 | 1.0 Ref. | 16/116 | 1.0 Ref | 9/116 | 1.0 Ref. | 15/116 | 1.0 Ref. |
| | *Lyc/Gln* | 8/146 | 1.06 (0.38–2.96) | 10/146 | 0.50 (0.20–1.21) | 19/146 | 1.68 (0.69–4.18) | 44/146 | 2.33 (1.19–4.63) |
| | *Gln/Gln* | 4/38 | 1.94 (0.57–6.53) | 2/38 | 0.41 (0.10–1.72) | 5/38 | 1.61 (0.57–4.55) | 22/38 | 4.48 (1.99–10.18) $P = 0.0000979$ |
| 6–10 year | *Lyc/Lyc* | 1/116 | 1.0 Ref. | 1/116 | 1.0 Ref | 2/116 | 1.0 Ref | 8/116 | 1.0 Ref. |
| | *Lyc/Gln* | – | – | 4/146 | 3.12 (0.35–7.54) | 4/146 | 1.57 (0.29–8.44) | 1/146 | 0.11 (0.01–0.80) |
| | *Gln/Gln* | 1/38 | 3.0 (0.19–46.84) | – | – | – | – | 2/38 | 0.77 (0.17–3.50) |
| >10 year | *Lyc/Lyc* | – | – | 1/116 | 1.0 Ref | – | 1.0 Ref. | 1/116 | 1.0 Ref. |
| | *Lyc/Gln* | – | – | 2/146 | 1.58 (0.15–17.22) | – | – | – | – |
| | *Gln/Gln* | – | – | – | – | 1/38 | – | 1/38 | 3.00 (0.19–46.84) |

OR was calculated by Epi-Iinfo. Version 3.5.1 (Center for Disease Control and Prevention)

*S* stages, *n/c* genotype at particular stage to number of control for the same genotype, *OR* odds ratio, *95% CI* confidence interval

Only significant *P* value is given

## Discussion

Apart from the NER pathway for repairing adducted DNA, the *ERCC2* gene is involved in degradation of viral cDNA, polymorphism in this gene might have reduced effect on viral cDNA degradation, whereby viral replication would be successful and reduces CD4 count to promote HIV disease progression to AIDS. This is the first study that has attempted to find out the association of *ERCC2 Lyc*$^{751}$*Gln* polymorphism with HIV/AIDS disease progression. In fact it has been reported that the presence of variant allele of this gene is associated with an increased risk of cancers such as melanoma [29], prostate [30], bladder [31], oesophagus [32] among others. However, conflicting reports have also been available with respect to different cancer types: bladder [33], breast [34, 35] and lung [36].

The *Gln/Gln* genotype frequency showed significant variation between cases and controls suggesting a possible role of disease susceptibility in cases. Moreover, this genotype was found to be associated with rapid disease progression in 3–5 years seroconvertor category.

The present finding indicated that the *Gln/Gln* genotype has impact on HIV-1 susceptibility and play role in disease progression to AIDS, the *Lyc/Gln* genotype too showed association with stage and risk of accelerated disease progression. Yoder et al. [18] indicated that *XPD* and *XPB* mutant cells have high transduction of viral cDNA indicating reduced role of these two mutated genes in degrading viral cDNA. It is consistent with the present study where the variant *Gln/Gln* genotype of *ERCC2* gene was significantly associated with disease susceptibility and progression due to the reduced role of the ERCC2 protein in viral cDNA degradation, thereby, increasing the pool of available cDNA for integration and ultimately promoting low immune response to opportunistic infection. Actually this finding needs to be confirmed with large cohort study by including other disease progression measures like viral load, and other clinical and molecular markers. Likewise, the physiological process, how the variant genotype facilitates susceptibility and disease progression in HIV infection needs to be explained by testing in vitro experiments, though it is ascertained that the *ERCC2 Lyc*$^{751}$*Gln* polymorphism is predicted to affect protein function in nucleotide excision repairing pathway [21]. In addition, it has been observed that mutations in the *XPD* gene can diminish the activity of TFIIH complexes giving rise to repair defects, transcription defects, and abnormal responses to apoptosis. Because *XPD* is important in multiple cellular tasks and rare *XPD* mutations results in genetic diseases *XPD* polymorphism may operate as genetic susceptibility factor [37]. Furthermore, this gene may also participate in other regulatory cellular processes including DNA replication and basal transcription [38], cell cycle progression [39], and P53 mediated apoptosis [40, 41]. Due to this vital role of the *XPD* gene in the basic physiology of the cell, the *Gln/Gln* genotype might be playing a significant role for HIV susceptibility and disease progression. One of the drawbacks of this study was the failure to use exposed and un infected patients as controls, because it was too difficult to get the negative spouses of the patients (though their number was very small) due to various reasons, although some of the control individuals used in the study had reported experiencing of promiscuous sexual behavior [41].

Apart from the nucleotide excision repair role of *ERCC2*, this gene is linked with other roles like viral DNA degradation, basal transcription repair complex FIIH and p53 mediated regulator of apoptosis which could have effect on viral host interactions [42].

Retroviral DNA integration creates a discontinuity in the host cell chromatin and repair of this damage is required to complete the integration process. As integration and repair are essential for both viral replication and cell survival, it is possible that specific interactions with the host DNA repair systems might provide new cellular targets for human immunodeficiency virus therapy [43, 44]. One possible way of accomplishing this target effectively is through analyzing the role of host genetic factor in HIV disease susceptibility and progression.

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